## REMARKS/ARGUMENTS

Claims 1 - 29 are pending in the above-identified application. Claims 4 - 7, 10 - 12, 16, and 24 - 29 stand withdrawn from further consideration by the Examiner, 37 CFR 1.142 (b), as being drawn to a non-elected invention. Claims 1, 3 8 - 9, 13 - 15 and 17 - 23 have been acted upon by the Examiner. Claims 1, 9, 19 and 20 have been amended to point out the claimed invention with greater particularity. No new matter is added by these amendments. In light of these amendments and the remarks and arguments set forth below, Applicants respectfully request reconsideration of the application.

Rejections under 35 U.S.C. § 102:

Claims 1, 14, 17-19, and 23 remain rejected under 35 U.S.C. 102(b) as being anticipated by Sallusto *et al.*, 1994, *J. Exp. Med.* The Examiner continues to allege that Sallusto teaches a method for generating dendritic cells from peripheral blood mononuclear cells (*i.e.*, monocytic dendritic cell precursors) by culturing in GM-CSF in the absence of additional cytokines. Furthermore, the Examiner continues to allege that the disclosed said dendritic cells are immature, as evidenced by their expression of CD11c and MHC, but the lack of expression of B7. Still further, the Examiner continues to allege that the monocytic dendritic cell precursors used to generate the immature dendritic cells were non-activated (*i.e.*, were isolated on a percoll gradient without positive selection or other stimulation). Additionally, the Examiner continues to allege that the differentiated dendritic cells of Sallusto were contacted with a bacterial antigen (tetanus toxoid) for a time period sufficient for antigen uptake, as evidenced by their ability to stimulate tetanus toxoid specific T cells.

The Examiner has considered Applicant's prior arguments and the declaration of one of the inventors (the Bosch Declaration), but did not find them persuasive. In particular, although Applicant has submitted evidence of the fact that the cells obtained by Sallusto *et al.* by culture in GM-CSF alone are not dendritic cells, the Examiner maintains that Sallusto *et al.* have

performed all the steps of the claimed method, and therefore must have inherently obtained immature dendritic cells.

Applicants disagree with the conclusions of the Examiner. Sallusto *et al.* do not carry out all of the step of the claimed methods, because the manner in which the monocyte dendritic cell precursors are isolated and cultured by Sallusto *et al.* activates the monocyte dendritic cell precursors. This activation necessitates the addition of IL-4 by Sallusto *et al.* to prevent the differentiation of the monocytic dendritic cell precursors into macrophage. Applicants were not arguing that Sallusto *et al.* teach away from using GM-CSF alone to obtain immature dendritic cells as much as the reference does not teach all of the steps.

The Examiner also alleges that it is well established that dendritic cells are a heterogeneous cell population that exist as many different subtypes with different surface phenotypes. Lutz *et al.*, 1999 (of record) has been cited by the Examiner as teaching a population of immature dendritic cells that express CD11c, but essentially do not express B7. WO03/010292 (of record) has been cited by the Examiner as teaching that immature dendritic cells are $CD11c^{+}$ and CD86 (B7) negative. Still further, the Examiner alleges that the existence of dendritic cell subsets that are negative for CD1a is known in the art citing Freudenthal *et al.*, page 7701, O'Doherty *et al.*, page 1073, and WO 03/010292 pages 27-28, (all of record). The cells taught by Sallusto *et al.* express CD11c, which the Examiner alleges is well established as a specific marker of dendritic cells. The instant claims are not limited to immature dendritic cells that express CD1a or high levels of B7, and based on the state of the art, a cell that expresses CD11c, MHC, and B7 at a level of +/- would be considered an immature dendritic cell.

Applicants have reviewed the various references cited by the Examiner and do not believe that on whole the references support the position of the Examiner, but in an effort to further expedite prosecution of the certain subject matter disclosed in the specification claim 1 has been amended to recite [a] method for differentiating monocytic dendritic cell precursors into immature dendritic cells having CD1a on the cell surface, comprising: a) providing a cell population comprising non-activated monocytic dendritic cell precursors; and b) contacting the

non-activated monocytic dendritic cell precursors in a culture vessel with a dendritic cell culture media supplemented with granulocyte-macrophage colony stimulating factor in the absence of additional cytokines under conditions that do not activate the monocytic dendritic cell precursors for a time period sufficient for the monocytic dendritic cell precursors to differentiate into immature dendritic cells having CD1a on the cell surface. In addition, claims 19 and 20 have been amended to clarify that the immature dendritic cells have CD1a on the cell surface to be consistent with claim 1.

The Examiner has also concluded that Applicants argument that an inherency argument cannot be relied upon, because precursor cells taught by Sallusto *et al.* are not "non-activated", as recited in the instant claims is not persuasive. It is alleged by the Examiner that Applicants particularly argue that the precursor cells can be "activated" by adherence to plastic, and that even if the density gradient isolated precursors of Sallusto *et al.* are not purified by adhesion, they would adhere to the plastic substrate used for subsequent culture. The Examiner does not believe that the instant specification defines the term "non-activated". For example, even plastic adherent cells might be considered "non-activated" if they have been cultured in the absence of any direct stimulus. Moreover, the Examiner alleges that the monocytic precursor cells taught by Sallusto *et al.* were isolated directly from blood by density gradient centrifugation and negative selection without any type of cell stimulation (including adherence to plastic), and can be considered "non-activated". In addition, the Examiner has dismissed Applicant's argument regarding the asserted subsequent adherence of the precursors to plastic during culture with cytokines as irrelevant because the instant claims are not limited in this regard.

Applicants have reviewed the Examiner's rebuttal to the arguments that have been filed previously and strongly disagree with the conclusions. As above, without acquiescing to any remark made by the Examiner, claim 1 has been amended to point out the claimed invention with greater particularity. In particular, the immature dendritic cell produced by the claimed method has CD1a on the cell surface. The "dendritic cell" produced by Sallusto *et al.*, which even the authors do not characterize as an immature dendritic cell, does not express CD1a. In addition, as above, claims 19 and 20 have been amended to point out with particularity that the

immature dendritic cells produced by the method of the invention express CD1a on their cell surface. As such, Applicants believe the amendments to claim 1 obviate the rejection of the Examiner.

Claims 3, 8 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto *et al.*, 1994, *J. Exp. Med.* (*supra*), in view of Bernard *et al.*, 1998, *Hem. Cell. Ther.* The teachings of Sallusto are described above. The Examiner alleges that although Sallusto does not culture in a low avidity culture vessel comprising PFTE, Bernard teaches a method to generate dendritic cells from purified blood monocytes by culturing in a TEFLON™ (*i.e.*, comprising PFTE) bag. Furthermore, the Examiner alleges that Bernard teaches that the method meets good laboratory practice (GLP) procedures necessary for the clinical use of dendritic cells. It is based on these alleged teachings that the Examiner concludes it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using the TEFLON™ culture vessel, as taught by Bernard. The Examiner believes that the ordinary artisan at the time the invention was made would have been motivated to do so, since Bernard teaches that this method is useful for clinical purposes, since it involves the large scale differentiation of dendritic cells in a culture system that meets GLP procedures and that the artisan of ordinary skill would have had a reasonable expectation of success.

Applicants must again respectfully disagree with the rejection of claims 3, 8 and 9 on the above basis. In particular, as above Sallusto reference does not teach or suggest a method for producing immature dendritic cells using GM-CSF alone. The claims as amended point out with greater particularity that the immature dendritic cells produced by the method of the invention express CD1a. As such, this method is not disclosed or suggested by Sallusto *et al.* Given that the primary reference does not disclose or suggest the present invention, the combination with Bernard *et al.* can not disclose or suggest the invention encompassed by claims 3, 8 and 9. Applicants therefore respectfully request the Examiner reconsider and withdraw the rejection of claims 3, 8 and 9 as unpatentable over Sallusto *et al.* in view of Bernard *et al.*

Claim 13 and 20-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto *et al.*, 1994, *J. Exp. Med.* (*supra*), in view of Bosch *et al.*, 2001, *J. Invest. Derm.*, meeting abstract. As set forth previously, the teachings of Sallusto are described above. The Examiner has acknowledged that Sallusto *et al* does not teach generating immature dendritic cells in serum free medium, nor maturing dendritic cells with IFN-γ and BCG, but the Examiner alleges that Bosch teaches that dendritic cells can be successfully generated in serum free medium, and that dendritic cells can be matured with a combination of IFN-γ and BCG. Furthermore, the Examiner alleges that Bosch teaches that dendritic cells are extremely useful for therapeutic purposes, and that the serum free culture medium (in contrast to the FBS containing medium taught by Sallusto) complies with the good manufacturing practice conditions that are required for clinical trials. Additionally, the Examiner alleges that Bosch teaches that maturation with IFN-γ and BCG results in a dendritic cell population that can induce a immune response against a tumor antigen in cancer patients. It is therefore the Examiner's conclusion, that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using serum free medium, as taught by Bosch and that the ordinary artisan at the time the invention was made would have been motivated to use serum free medium, since Bosch teaches that dendritic cells are extremely useful for therapeutic purposes, and that the serum free culture medium (in contrast to the FBS containing medium taught by Sallusto) complies with the good manufacturing practice conditions that are required for clinical trials. Furthermore, the Examiner believes that it would have been obvious to one of ordinary skill in the art to mature the dendritic cells, as taught by Sallusto, with BCG and IFN-γ as taught by Bosch and that the ordinary artisan would have been motivated to do so, since Bosch teaches that IFN-γ and BCG are extremely potent maturation agents that result in a dendritic cell population that can induce a immune response against a tumor antigen in cancer patients. Moreover, the Examiner believes that one of ordinary skill in the art would have a reasonable expectation of success, since Bosch teaches the effectiveness of these techniques in the generation of dendritic cells.

Applicants must again respectfully disagree with the rejection of claims 13, and 20-22 on the above basis. In particular, as above Sallusto references do not teach or suggest a method for producing immature dendritic cells using GM-CSF alone. The claims as amended point out with greater particularity that the immature dendritic cells produced by the method of the invention express CD1a. As such, this method is not disclosed or suggested by Sallusto *et al.* Given that the primary reference does not disclose or suggest the present invention, the combination with Bosch *et al.* can not disclose or suggest the invention encompassed by claims 13, and 20-22. Applicants therefore respectfully request the Examiner reconsider and withdraw the rejection of claims 13, and 20-22 as unpatentable over Sallusto *et al.* in view of Bosch *et al.*

Claim 15 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto *et al.*, 1994, *J. Exp. Med.* (*supra*), in view of Lewalle *et al.*, 2000, *J. Immunol. Methods*. The teachings of Sallusto *et al.* are described above. The Examiner acknowledges that Sallusto *et al.* does not teach using a cryopreserved cell population to generate dendritic cells. But the Examiner alleges that Lewalle *et al.* teaches the generation of dendritic cells from frozen peripheral blood mononuclear cells. Furthermore, the Examiner alleges that Lewalle *et al.* teaches that many clinical protocols are based on sequential injections of dendritic cells, and therefore it would be of practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes. From these alleged teachings the Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using frozen peripheral blood mononuclear cells, as taught by Lewalle and that the ordinary artisan at the time the invention was made would have been motivated to do so, since Lewalle teaches that many clinical protocols are based on sequential injections of dendritic cells. Furthermore, the Examiner concludes that the ordinary artisan would have had a reasonable expectation of success since Lewalle *et al.* teaches that dendritic cells derived mononuclear cells in frozen peripheral blood retain their functional capacity.

Applicants must again respectfully disagree with the rejection of claim 15 on the above basis. In particular, as above Sallusto reference does not teach or suggest a method for

producing immature dendritic cells using GM-CSF alone. The claims as amended point out with greater particularity that the immature dendritic cells produced by the method of the invention express CD1a. As such, this method is not disclosed or suggested by Sallusto *et al.* Given that the primary reference does not disclose or suggest the present invention, the combination with Lewalle *et al.* can not disclose or suggest the invention encompassed by claim 15. Applicants therefore respectfully request the Examiner reconsider and withdraw the rejection of claim 15 as unpatentable over Sallusto *et al.* in view of Lewalle *et al.*

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 9 November 2007 By: Brian W. Poor

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